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Onset and relapse of juvenile dermatomyositis following asymptomatic SARS-CoV-2 infection

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Dear Editor, SARS-CoV-2 infection drives a marked inflammation, and has been described to precede the appearance in rare occasion of various autoimmune and inflammatory diseases including clinical, radiological, muscle biopsy and serological features consistent with dermatomyositis [1,2]. A working hypothesis is that juvenile dermatomyositis (JDM) is a type 1 interferon driven inflammatory response, triggered by one or more environmental stimuli, such as infection. In order to test the hypothesis that SARS-CoV-2 could promote JDM, we studied SARS-CoV-2 infection history in the 10 JDM patients with disease onset (n=6) or relapse (n=4) seen in our center since the start of the pandemic. IgG and IgM directed against 5 different portions of the virus were measured in patients plasma at the time of diagnosis: Whole spike protein, spike Receptor Binding Domain (RBD), spike S2 subunit, nucleocapsid protein (NP) and a Membrane-Envelope fusion glycoprotein (ME) [3]. Out of the 10 patients, we identified high titers of both IgG (**Figure 1a**) and IgM (**Figure 1b**) antibodies directed against SARS-CoV-2 proteins in one new onset (P1) and one relapsing patient (P2) (**Figure 1a**) indicating a recent history of infection by SARS-CoV-2.

P1 is a 15-year-old girl that developed a JDM associating poor general state, fatigue, weight loss, symmetrical polyarthritis, mild proximal muscle weakness and skin features: erythema and papule at the joint extensors, erythema and painful hyperkeratosis papules palmar and plantar, purple eyelids, and telangiectasia at the root of nails and gingival margins. Muscle biopsy's features were consistent with the diagnosis of JDM. Creatine kinase (CK) was elevated 545 U/L (<150). She was negative for muscle specific autoantibodies (MSAs). ~~No auto-antibodies were detected.~~ Interferon- α protein (IFN α 2) in the plasma, measured by Simoa assay (Quanterix Homebrew)[4] was markedly elevated (73476 fg/ml) (**Figure 1c**). Concomitant infection by SARS-CoV-2 was demonstrated by positive nasopharyngeal antigenic test two weeks before JDM onset and high IgG and IgM titer against whole spike protein, RBD and S2

two weeks after JDM onset (**Figure 1 a and b**). Treatment with intravenous immunoglobulins, corticosteroids and Tofacitinib 5mg b.i.d led to remission of the disease.

P2 is a 12-year-old girl who developed a skin relapse of typical JDM diagnosed 8 years earlier. At diagnosis she presented with mild muscle involvement and CK level was normal. Muscle Magnetic Resonance Imaging showed muscle oedema and muscle biopsy's features were consistent with the diagnosis of JDM. There were no MSAs detected. Cutaneous lesions consisted of erythema and Gottron's papule at the joint extensor, erythema and painful hyperkeratosis papules palmar and plantar, heliotrope eyelids, erythema and edema of the ears, shawl sign with flagellate erythema. Treatment with corticosteroids and methotrexate led to a complete remission of 8 years including 6 years off-therapy. Two weeks after being in contact with a COVID-19 positive family member, she experienced a purely skin relapse of the disease. Cutaneous involvement was similar to the lesions observed at initial diagnosis of JDM. No muscle involvement was noted and MSA remained absent. IFN α 2 concentration was markedly elevated at diagnosis (4612fg/ml) (**Figure 1c**). The presence of anti SARS-CoV-2 RBD, S2 and whole spike protein IgM in the plasma 2 weeks after onset of the symptoms, along with limited IgG, followed by increased levels of IgG and decrease of most IgM at week 6 suggest that the infection occurred at the same time as the JDM relapse (**Figure 1d**). Treatment with intravenous immunoglobulins and corticosteroids led to skin lesions remission and progressive decrease of IFN α 2 concentration: 1466fg/ml 10 weeks after the relapse.

~~Of note, P9 had 8 weeks after onset of his JDM high titer of IgM isotypes and an absence of detectable levels of IgG isotypes directed against any of the tested domains of SARS-CoV-2 (**Figure 1a and b**), what strongly suggest that SARS-CoV-2 infection happened after the JDM onset.~~

Altogether, out of the 10 patients with JDM-onset or relapse of JDM features seen in our center between April 2020 and March 2021 we identified 2 (20%) with a concomitant history of

SARS-CoV-2 infection. These patients had features consistent with typical JDM, according to the ENMC 2018 dermatomyositis classification criteria [5]. Considering that skin manifestations were completely similar at relapse and at diagnosis in P2, we think that the cutaneous involvement is mostly related to JDM rather than to SARS-CoV2 *per se*. Importantly, no other documented environmental stimulus temporally associated with the manifestations of JDM has been documented in these patients. A few cases of COVID-19-related-myositis have been previously reported and may be attributable to direct myocyte injury or to induction of autoimmunity [1,2]. Although the precise role of IFN α in the pathophysiology of JDM still needs to be deciphered, it is interesting to note that P1 and P2 had very high levels of circulating IFN α 2 compared to the median value (491fg/ml) in 33 patients with active JDM followed in our clinical center (150- and 9-fold increase, respectively) (**Figure 1c**). Altogether, these data strongly suggest that SARS-CoV-2 infection could trigger the development of JDM, possibly through induction of IFN α . Moreover, given that both patients were asymptomatic for COVID-19 symptoms, our observation also suggests that viral induction of JDM might be more frequent than expected as it could occur in patients without any manifestation of viral infection. Systemic evaluation of recent SARS-CoV-2, and other virus infection in newly diagnosed or relapsing patients would help to estimate the extent of this observation.

Declarations

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Conflicts of interest/Competing interests:

The authors had no competing interests to declare.

Availability of data and material

Results from all IgG and IgM dosages presented in this study are in supplementary table 1.

Authors' contributions:

MPR, BBM : Conceptualization, Methodology, Resources, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **SP, VB, MW, DD**: Formal analysis, Methodology, Resources, Validation, Investigation, Data curation, Writing - review & editing **AF**: Validation, Investigation, Original draft, Writing - review & editing. **AWM, IM, LCVW, EM, JLC, MAA, JPH, JB**: Resources, Validation, Investigation, Writing - review & editing. **CG**: Conceptualization, Methodology, Resources, Investigation, Validation, Writing - review & editing.

Ethical approval information

This study was approved by the CPP Sud est V: N° EudraCT : 2018-A01358-47 / 1.

Consent to participate

Patients and parents provided consent to participate to this study

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Figure 1: **a)** Dosage of anti SARS-CoV-2 whole Spike protein, RBD, S2, NP and ME IgG and **b)** IgM measured in relative antibody units (RAU) in the plasma of 10 patients with JDM onset or relapse diagnosed since the beginning of the pandemic in France. **c)** Quantification of IFN α 2 protein in the plasma of 33 active JDM patients followed in our clinical center (median: black dotted line), of P1 two weeks post onset and of P2 two weeks post relapse. **d)** Dosage of anti

SARS-CoV-2 whole spike protein, RBD, S2, NP and ME IgG and IgM at week 2 and week 6 post JDM relapse in P2 measured in relative antibody units (RAU).

